REMARKS/ARGUMENTS

Reconsideration of the above-identified application respectfully requested.

Rejection on Formal Grounds

Claim 20 is rejected under the provisions of 35 U.S.C. § 112, second paragraph, as being indefinite for being dependent from a cancelled claim. Since claim 17 was dependent from claim 13, claim 20 currently is amended to depend from claim 13. Thus, this inadvertent dependency error now is corrected.

Additional Claim Amendments

Independent claims 1, 6, and 10 have been amended to clarify that the "cyclodextrin" is "one or more of α-, β- or γ- cyclodextrin" consistent with the original application at, *inter alia*, p. 2, ll. 2-3; p. 5, ll. 11-22; and the working examples. Such clarification was deemed appropriate since several chemically modified forms (*e.g.*, methyl, dimethyl, and hydroxypropyl-cyclodextrins) have been reported in the art. The clarification merely recognizes that Applicants described and claimed a "cyclodextrin" complex and not a "modified cyclodextrin" complex. It is believed that this clarification will materially advance prosecution of this application.

No new matter is added by virtue of these claim amendments. Moreover, no claims have been narrowed with the meaning of *Festo* (*Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 US 722, 112 S.Ct. 1831, 152 L.Ed.2d 944, 62 USPQ2d 1705 (2002)). See also *Interactive Pictures Corp. v. Infinite Pictures Inc.*, 274 F.3d 1371, 61 USPQ 1152 (Fed. Cir. 2001) (addition of the words "transform calculation" was not a narrowing amendment because that addition did nothing more than make express what had been implicit in the claim as originally worded).

The Art Rejections

Claims 1, 4, 5, 6, and 9 stand finally rejected under the provisions of 35 U.S.C. § 102(b) as being anticipated by Iijima (JP 59-047202).

Claims 2, 3, and 4 stand rejected under the provisions of 35 U.S.C. § 103(a) as being unpatentable over Patel (U.S. Patent No. 5,569,463), Iijima, and Miyao (JP 60-089442).

Claims 10-12, 15-16, and 19 stand finally rejected under the provisions of 35 U.S.C. § 102(a) as being anticipated by Iijima.

Applicants respectfully traverse the rejections of the claims and grounds therefor.

Allowable Claims

Claims 7-8. 13-14, 21, and 22 are deemed allowable if written in independent form.

The Iijima Citation

Iijima teach a water-soluble freeze-dried coenzyme Q-10/dimethylbeta-cyclodextrin complex. Applicants describe, enable, and claim a water dispersible α-, β- or γ-cyclodextrin complex of coenzyme Q-10. The invention does not require dissolution of the cyclodextrins or CoQ-10 for complexation.

Iijima does not teach the skilled artisan about the inventive complexes, nor the unexpected properties, for example achieved by their freeze-dried preparation compared to spray drying or vacuum drying.

Iijima, rather, teaches the complexation of dimethyl-beta cyclodextrin with coenzyme Q-10 and not beta-cyclodextrin. Dimethyl-β-cyclodextrin, prepared by selective methylation of β-cyclodextrin, has entirely different properties as compared to β-cyclodextrin, in terms of its hydrophobicity, solubility, and complexation ability. Dimethyl β-cyclodextrin is soluble in water at room temperature as compared to the sparingly soluble β-cyclodextrin (1.8g /100ml water) and the solubility decreases with increasing temperature. In general, dimethyl-β-cyclodextrin forms water-soluble inclusion complexes with lipophilic compounds at room temperature. The CoQ-10/ dimethyl-β-cyclodextrin complex, according to Iijima, is water soluble as compared to the water dispersible β- and γ-CoQ-10 complexes of the present invention.

Applicants agree with the Examiner that both beta and dimethyl beta cyclodextrins have seven glucose units. But the methyl group substitution of all C2 secondary and C6 primary hydroxyl groups in the dimethyl derivative results in alterations in chemical and physical properties of the compound, as well as the biological activity in terms of toxicity. For example, Jansen *et al.* (1990) have reported that dimethyl beta-cyclodextrin is not suitable for eye-drop formulations as it is toxic to the corneal epithelium, while hydroxypropyl beta-cyclodextrin, another water soluble derivative of beta-cyclodextrin, was well tolerated at the same concentrations ("Beta-cyclodextrins as vehicles in eye-drop formulations: an evaluation of their effects on rabbit

comeal epithelium", Jansen T, Xhonneux B, Mesens J, Borgers M., *Lens Eye Toxic Res.*, 7 (3-4): 59-68, 1990).

Applicants have submitted a number of references illustrating the differences in the complexation behavior of dimethyl beta and beta cyclodextrin (refer to page 6-7, Amendment dated May 31, 2005). With the clarifying amendments submitted herewith, there now is no doubt that Applicants and Iijima are dealing with different cyclodextrins having different properties and which form different complexes with CoQ-10.

Iijima proposes a method for making the CoQ-10/dimethyl-β-cyclodextrin complex containing 1% CoQ-10 in the freeze-dried product. The low level of CoQ-10 makes incorporation of therapeutic concentrations (30-100 mg CoQ-10 per day) in the dosage forms (hard gelatin capsules, tablets) expensive and not viable in the supplement industry. It also is not practical using tablet or capsule processing; for example, it requires 3 g of powder/capsule to obtain a dose 30 mg of CoQ-10.

Iijima also teach the formation of an aqueous solution of the CoQ-10 complex whereas Applicants describe a solid dispersion. The differences are significant when we consider a commercially viable process. Iijima describes a 10% solution containing 1% CoQ-10. The low levels of total solids and CoQ-10 makes any drying process very expensive on a commercial scale when the oral dosages require 30 mg CoQ-10/capsule. Iijima's product is suitable for a injectable form of CoQ-10.

Thus, Iijima teaches the skilled artisan only about dimethyl-β-cyclodextrin. The invention is teaching the skilled artisan about and claiming α-, β-, and γ-cyclodextrins. These compounds do not have the same chemical properties when it comes to hydrophobicity, solubility, and complexation ability. These properties, however, are the precise properties of interest in making CoQ-10 complexes. In reality, then, Iijima teaches the skilled artisan nothing about the inventive complexes, nor the unexpected properties, for example, achieved by their freeze-dried preparation compared to spray drying, evaporation, *etc.* Clearly, Iijima totally fails to teach the present invention as required for a § 102(b) rejection. This rejection, then, must be withdrawn.

The Patel Citation

Patel proposes improved delivery systems for pharmaceutical ingredients. The delivery system includes a solid carrier, the solid carrier being formed of different combinations of the pharmaceutical active ingredients, hydrophilic surfactants, lipophilic surfactants, and triglycerides. They mention cyclodextrins as one of the solubilizers

among a number of ingredients. The examples illustrate formation of coated beadlets, seal coating, protective coating, or enteric coating of the beadlets, none of which use cyclodextrins or CoQ-10. The examples do not use freeze-drying as a means to obtain dry powders. Patel also does not teach formation of a molecular complexation between CoQ-10 and cyclodextrins or an efficient drying method for any complex.

It is well known in the art that hydrophobic compounds present delivery challenges because of their physicochemical properties. The problems associated with CoQ-10 absorption and the need of developing delivery system also is well known in the industry. Hence, Patel does not offer any specific motivation to produce a CoQ-10 cyclodextrin complex.

Even assuming that Patel teaches what the Examiner alleges, combining Patel with Iijima will not result in the present invention, because Iijima does not teach the particular cyclodextrins that Applicants disclose, enable, and claim.

The Miyao Citation

Miyao teaches the complexation of γ-cyclodextrin with CoQ-10. Miyao uses an aqueous medium, and the mixture is stirred for 67 hours, followed by suction filtration, air drying, and washing with ether, followed by drying. The example indicates ~50% loss in the recovery of the product. It is not obvious from the teachings of Miayao that an economical, commercially viable product can be produced, especially in a cost-conscious supplement industry. Cyclodrextrins in general are expensive and γ-cyclodextrin is the most expensive (currently about $50-$100 per kg). CoQ-10 also is an expensive ingredient (currently about $2800-$5000 per kg) and there is a limited worldwide production; hence, a 50% loss in the final product recovery is commercially unacceptable.

Miyao teaches two different methods of preparation of its complex: the kneading method and the solution method (see 4th and 5th paragraphs, p. 3, English translation). Now, Miyao's examples show a solution process the includes, *inter alia*, suction filtration, water washing, drying at 70° C, water washing, ether washing, and drying again. Only a 50% recovery of product complex results. Such a process is not amenable to commercial scale-up, in part, due to the low recoveries and use of volatile (potentially explosive) ether wash.

Applicant, on the other hand, uses an aqueous dispersion technique for preparing its complex. Applicant's chosen process employs a cyclodextrin aqueous

dispersion homogenized with CoQ-10 (crystals) followed by refrigerated storage to complete the reaction. The complex can be recovered by any conventional technique, such as, freeze-drying resulting in unexpectedly high yields of product complex. Applicant's process is amenable to commercial-scale up and, in fact, already is commercial in this form.

In the present application, then, Applicants have described a highly efficient, commercially viable method for the production of the CoQ-10 inclusion complex with γ- and β-cyclodextrins containing up to about 20%–24% CoQ-10. The process does not include prolonged stirring, suction filtration, or use of highly volatile solvents. The recovery of the product ranges between about 85%–95%, based on the drying method used. With the high prices of the reactants, such high recovery rates are especially valuable and telling of the patentability of the present invention.

Thus, adding Miyao (even assuming it to teach what the Examiner alleges) to Iijima/Patel does not render obvious the present invention, because Iijima does not teach the particular cyclodextrins that Applicants disclose, enable, and claim.

Summary

In view of the remarks and claim amendments submitted herewith, allowance of the claims and passage to issue of this application respectfully requested.

Respectfully submitted,

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CERTIFICATE OF FACSIMILE TRANSMISSION

I hereby certify that this correspondence is being sent on June 2, 2005 to the Director of Patents and Trademarks at 703-872-9306.

Jane Keeney